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Epidemiological Association between Some Dietary Habits and the Increasing Incidence of Type 1 Diabetes Worldwide

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Key Words
Gene-nutrient interactions · Type 1 diabetes · Nutritional epidemiology

Abstract
Background/Aims: The variation in incidence of type 1 diabetes (T1D) worldwide is genetically based. However, its increasing incidence is environmentally determined. Our aim was to describe the role of nutritional habits and of gene-nutrient interactions in the rising incidence of TID. ***Methods:*** We did an ecological study in the 37 world areas were a 3% yearly increase of T1D incidence had been reported, and we calculated through the FAO's Food Balance Sheets the per caput daily supply of milk, meat and cereals from 1961 to 2000 and its correlation with the TID incidence. ***Results:*** The supply of milk and cereals remained almost unchanged, whereas that of meat increased by over 31%. The absolute mean TID increase (number of cases per 100,000 per year) was + 0.32. A significant positive correlation with supply of milk was present from 1961 to 2000, while that with meat and cereals became significant in 1983 and 2000. ***Conclusion:*** Our ecological analysis indicates that nutritional factors, and in particular meat consumption, play a role in the incidence of T1D and its increase worldwide. Further experimental and case-control studies are warranted in order to assess the gene-nutrient interactions.

Introduction

Type 1 diabetes mellitus (T1D) results from an organ-specific, T cell-mediated autoimmune destruction of the pancreatic beta cells [1], as a consequence of genetic [2] and environmental [3, 4] factors acting together.

The worldwide variation in incidence (per 100,000 per year) of T1D among children aged 0–14 years ranged in the 1990s from 0.1 in China and Venezuela to 36.8 and 36.6 in Sardinia and Finland, respectively, reflecting the different degrees of genetic susceptibility of populations [5], to which environmental factors are superimposed as inducers or triggers [6, 7]. This determines the frequency of T1D in the different areas of the world [8–10].

The polygenic nature of susceptibility to T1D [11]; the chromosomal regions where genes IDDM1 to IDDM15 are located [12]; the class I and II molecules of the human histocompatibility leukocyte antigen (HLA) [13]; the reasons for the susceptibility associated with DR3 and DR4 and the protection afforded by DR2 [14, 15]; the distribution of the DQ alleles among resident and migrant populations [16–18] have been fully reported and discussed in our recent review [19].

A dramatic increase in T1D incidence worldwide took place in both low- and high-incidence populations [20–24], ranging from 3.0% [22] through 3.2% [24] to 3.4% [23] per year over the past decades. This phenomenon is likely to stem from interaction between non-genetic fac-

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tors and genetic susceptibility [25]. Among the former, viral infections, toxins and nutritional factors are the best candidates [3, 26, 27].

Here we present evidence that nutritional habits and gene-nutrient interactions are involved not only in the incidence of T1D [27], but also in its rise in the second half of the 20th Century. The knowledge of the genetic background of the disease [19] will come essential to the understanding of such gene-nutrient interactions.

Methods

The incidence (per 100,000 per year) of T1D among children in 37 areas of the world [22] was our starting point. In 30 areas the age of children ranged from 0 to 14 years, and in other 7 from 0 to 15, 16, 17 and 19 years. The mean level of incidence referred to the calendar year 1983, and the increase in incidence (% per year) was expressed on a logarithmic scale through the variable length (mean: 14.9 years) of the pertaining study periods between 1960 and 1996.

Two further elaborations of the above-mentioned data were made.

The first one was necessary in order to line up the variable beginning and end of the incidence studies; it consisted in the extrapolation of the straight lines of the logarithmic incidence [22] to the calendar years 1961 and 2000. The reasons for this choice are discussed below.

The second elaboration was the calculation of the absolute increase in incidence, i.e. the increased number of cases per 100,000 per year and the 95% confidence intervals (CIs) in each of the 37 areas. These calculated data, ordered according to the descending value, are reported in the last (right) column of table 1, beside the columns of incidence and % increase of it, taken from [22].

The nutritional habits of the 37 populations were assessed through the Food Balance Sheets of the Food and Agricultural Organization (FAO) in 1961 (the first year in which the electronic FAO's sheets were available), 1983 (the mean level of incidence, covered by almost all studies [22]), and 2000 (the end of the 20th Century) [28]. In particular, the per caput supply per day of energy (kcal) as milk (plus dairy products, excluding butter), meat and cereals was obtained for each country. These data are reported in table 2.

Statistical Analysis

Using the calculation of correlation coefficients between the log-transformed incidence in 1983 and the relative increase in incidence, as reported in [22], we substituted the relative (%) for the absolute (number of cases) increase in incidence per year, and calculated the correlation coefficient r and its significance.

The changes in food items supply from calendar years 1961 to 1983 and to 2000 were calculated as means, SD and SEM. For assessment of their significance the paired t test and the corresponding p were used.

A correlation analysis between TID incidence in the calendar years 1961, 1983 and 2000 and average per caput daily supply of milk, meat and cereals, respectively, was conducted and the correlation coefficient r, the t value and the p degree of significance were calculated. $p < 0.05$ was considered statistically significant and reported in bold in the tables. The software programme for the above calculation was MS Biostat statistical package (McGraw-Hill, copyright 1988).

We conducted also a univariate regression analysis with T1D incidence as the dependent variable and each of the country-specific dietary indicators and average annual temperature, gross domestic product (GDP), percentage employed in agriculture, and education expenses, as the independent variables. These data were obtained from publicly available resources and referred to the year 1983 (the year common to almost all studies). We then set up a multiple regression model (MANOVA), in which the variables that correlated with T1D incidence in the univariate analysis had the disease rate as the outcome.

Results

Besides the yearly relative (% ± 95% CIs) increase in T1D incidence in the 37 areas of the world [22], the calculated yearly absolute increase (the increased number of cases per 100,000 per year ± 95% CIs) in the same areas ranged from 0.94 in Australia West to –0.03 in Colorado, USA (table 1). While the relative annual change vs. basal incidence was + 3% ($r = –0.560$, $p = 0.0004$), the absolute increase was + 0.32 ($r = +0.521$, $p = 0.0001$).

In the univariate regression analysis, the geographic and socio economic variables correlated significantly with T1D incidence rate (average temperature: r –0.52, $p < 0.01$; GDP r 0.54, $p < 0.01$; percentage employed in agriculture r –0.40, $p < 0.05$; education expenses as a percentage of GDP r 0.38; $p < 0.05$). When, however, we fitted the regression model with all the covariates, the strength of the correlation was reduced to nonsignificant values, except for the three categories of food items (milk, meat and cereals) that remained significant, indicating the confounding effect of diet.

The per caput supply (kcal per day) of milk remained almost unchanged in the 37 areas from 1961 to 2000 (table 2). A strong, highly significant positive correlation with T1D incidence was already present in 1961 and persisted unchanged up to 2000 (table 3).

The per caput supply of meat in the 37 areas increased steadily and significantly from 1961 to 1983 and to 2000 (table 2). In the calendar year 1961 no correlation was found between meat supply and T1D incidence. The correlation became significant in 1983 and persisted in 2000 (table 3). When the 37 populations were split into two groups according to their high (the first 19) or low (the last 18) absolute increase in T1D incidence, in the former the meat consumption increased nonsignificantly from 1961 to 1983, whereas in the latter it increased significantly by

Table 1. Relative (%) and absolute (number of cases) yearly increase per 100,000 (± 95% CIs) in TID incidence in children 0–14 years in 37 populations: from Onkamo et al. [22], modified (see 'Methods')

Country: area	Incidence per 100,000 per year	Increase in incidence % per year	Absolute increase in n of cases per year
Australia: West	14.9	6.3 (2.11; 10.5)	0.94 (0.31; 1.56)
Canada: Prince Edward Island	23.5	3.2 (–0.33; 6.38)	0.75 (–0.08; 1.50)
UK: Leicestershire	7.8	9.5 (6.51; 12.53)	0.74 (0.51; 0.98)
Finland	30.3	2.3 (1.98; 2.57)	0.70 (0.60; 0.78)
UK: Oxford	18.5	3.7 (1.82; 5.50)	0.69 (0.34; 1.02)
Norway	20.8	3.2 (1.19; 5.22)	0.67 (0.25; 1.09)
New Zealand: Auckland	10.1	6.4 (4.20; 8.52)	0.65 (0.42; 0.86)
USA: Hawaii	7.8	7.8 (1.80; 14.87)	0.61 (0.14; 1.16)
Libya	8.7	6.3 (0.69; 11.80)	0.55 (0.06; 1.03)
UK: Scotland	21.6	2.5 (1.85; 3.08)	0.54 (0.40; 0.67)
Hungary	6.1	8.5 (6.50; 10.42)	0.52 (0.40; 0.64)
Slovakia	7.5	5.5 (3.64; 7.41)	0.41 (0.27; 0.56)
Poland: Krakow	5.9	6.8 (2.27; 11.41)	0.40 (0.13; 0.67)
UK: Plymouth	14.6	2.7 (0.91; 4.50)	0.39 (0.13; 0.66)
Algeria: Oran	4.7	7.9 (1.85; 14.00)	0.37 (0.09; 0.66)
New Zealand: Canterbury	12.7	2.7 (–0.05; 10.50)	0.34 (–0.06; 1.33)
France	8.0	3.9 (2.85; 4.94)	0.31 (0.23; 0.40)
Sweden	24.9	1.2 (0.42; 2.02)	0.30 (0.10; 0.50)
UK: Yorkshire	14.3	1.9 (0.30; 3.53)	0.27 (0.04; 0.50)
USA: Allegheny County	14.7	1.5 (0.21; 2.83)	0.22 (0.03; 0.42)
Austria	7.8	2.7 (1.58; 3.76)	0.21 (0.12; 0.29)
Poland: Wielkopolska	4.4	4.8 (1.94; 7.66)	0.21 (0.09; 0.33)
Iceland	9.0	2.3 (–2.38; 6.96)	0.21 (–0.21; 0.63)
Italy: Turin	8.4	2.2 (–3.99; 8.35)	0.19 (–0.34; 0.70)
East Germany	6.7	2.4 (1.96; 2.90)	0.16 (0.13; 0.19)
Israel: Yemenith Jews	5.0	3.2 (2.51; 3.88)	0.16 (0.13; 0.19)
Canada: Montreal	9.3	1.6 (–0.67; 3.82)	0.15 (–0.06; 0.36)
Bulgaria: East	6.3	2.1 (1.03; 3.15)	0.13 (0.06; 0.20)
Japan: Hokkaido	1.7	5.9 (4.14; 7.63)	0.10 (0.07; 0.13)
Malta	14.7	0.5 (–2.15; 3.19)	0.07 (–0.32; 0.47)
Lithuania	6.4	1.1 (–4.25; 6.41)	0.07 (–0.27; 0.41)
Latvia	7.2	0.9 (–1.90; 3.75)	0.06 (–0.14; 0.27)
Poland: Rzeszów	5.1	1.1 (–3.25; 5.40)	0.06 (–0.17; 0.28)
China: Shanghai	0.7	7.4 (2.30; 12:51)	0.05 (0.02; 0.09)
Estonia	10.2	0.4 (–0.96; 1.76)	0.04 (–0.10; 0.18)
Peru: Lima	0.5	7.7 (–0.97; 16.40)	0.04 (–0.05; 0.08)
USA: Colorado	12.3	–0.2 (–2.52; 2.19)	–0.03 (–0.31; 0.27)
Mean incidence	10.6		
Change globally		+3.0 % (2.59; 3.33) p = 0.0001	+0.32 (0.27; 0.35) p = 0.0001
r vs. basal incidence		–0.560 p = 0.0004	+0.521 p = 0.0001

over 46%, but nonetheless it didn't reach the level of consumption of the former (table 4).

The per caput supply of cereals in the 37 areas decreased non significantly from 1961 to 1983, then recovered almost completely from 1983 to 2000 (table 2). No significant correlation, but a definite negative trend existed in 1961 between per caput kcal from cereals and T1D incidence. A highly significant negative correlation was found in 1983 and to a lesser extent in 2000 (table 3).

Table 2. Mean per caput supply (kcal/day) of milk, meat, and cereals from 1961 to 2000 in 37 areas of the world

Year	kcal	SD	SEM	Difference	95% CIs	% difference	t	p
Milk								
1961	289.49	135.24	22.23					
1983	304.30	108.57	17.85	+14.81	–42.00 to 71.00	+5.12	0.519	0.605
2000[a]	289.11	100.21	16.47	–0.38	–55.54 to 54.74	–0.0013	–0.014	0.989
Meat								
1961	271.92	140.92	23.17					
1983	344.97	111.80	18.38	+73.04	14.10 to 132.00	+26.86	2.470	**0.016**
2000[a]	357.70	119.32	19.62	+85.78	25.27 to 146.29	+31.55	2.826	**0.006**
Cereals								
1961	1,004.92	346.75	56.99					
1983	934.14	318.88	52.44	–70.78	–225.15 to 83.58	–7.04	–0.914	0.364
2000[a]	990.54	260.07	42.85	–14.38	–156.52 to 127.76	–1.34	–0.202	0.841

[a] vs. 1961.

Table 3. Correlation coefficients r, two-tailed test t, probability value p between incidence of TID and consumption of milk, meat and cereals in calendar years 1961, 1983 and 2000 in 37 areas of the world

	Milk			Meat			Cereals		
	r	t	p	r	t	p	r	t	p
TID 1961	0.580	4.208	**0.000**	0.176	1.058	0.297	–0.306	–1.899	0.066
TID 1983	0.550	3.894	**0.000**	0.416	2.705	**0.010**	–0.567	–4.070	**0.000**
TID 2000	0.377	2.405	**0.022**	0.349	2.204	**0.034**	–0.331	–2.076	**0.045**

Table 4. Mean meat consumption (per capita, per year) in 19 areas with the highest absolute increase in T1D incidence vs. 18 areas with the lowest one, in 1961 and 1983

	Incidence areas		% difference	p
	19 high	18 low		
1961	334.11	206.28	–38.25	**0.040**
1983	385.16	302.56	–21.45	**0.022**
% difference	+15.28	+46.67		
p	0.205	**0.013**		

Discussion

The steady increase of T1D incidence in the second half of past century took place in both European [20–24] and non-European [21, 22] countries. A greater relative increase was recorded in children under 5 years of age [23, 24]; however, on an absolute scale the increase was similar for all ages under 15 years [24].

The issue of relative vs. absolute increase in T1D incidence should not be considered as a simple statistical artifice [29]. An inverse association between the percent increase and the level of basal incidence ($r = –0.560$, $p = 0.004$) was found [22], indicating that the relative increase was more pronounced in populations with low incidence and suggested a catch-up phenomenon [26]. If, however, the absolute increase (the increased number of cases per 100,000 per year) is calculated (table 1), just the opposite is found ($r = +0.521$, $p = 0.0001$), indicating that a greater number of extra cases occurred in populations with higher level of incidence and hence with higher proneness (either genetically determined or environmentally induced, or both) to T1D.

Among factors accounting for the wide variation in T1D incidence from country to country, the distribution of genetic susceptibility in relation to ethnic diversity is

the main determinant of the response of various populations to the environmental challenge [8–10]. However, the above-cited rapid increase in T1D incidence points to an important contribution of environmental factors. Dietary exposure early in life is likely to be involved in T1D risk, as pointed out by experimental studies in animal models such as BB rat [30] and NOD mouse [31], case-control [32] and epidemiological studies in humans [33]. The dietary risk can be turned into T1D also later, until puberty and adolescence, in both animals and humans [34].

Changes in nutritional habits of different populations are involved, in our opinion, in the increasing incidence of T1D in the second half of past century.

In the 37 populations, the per caput supply of milk remained nearly unchanged from 1961 to 2000 while its correlation with the incidence of T1D was statistically significant. A definite, statistically significant increase in per caput meat supply was evident from 1961 to 2000 and correlated positively with the incidence of T1D in 1983 and 2000, but not in 1961.

Since changes in consumption of milk, meat and cereals are correlated with increase in TID incidence at least in calendar years 1983 and 2000 (table 3), the same food items should be listed among environmental inducers or triggers of the disease. And, in actual fact, a number of data from literature support this role [19, 32, 33].

The mechanisms of involvement of nutrients in the pathogenesis of autoimmune diabetes have been fully reviewed by us [19]. Here we confine ourselves to recall some basic concepts about the dual consequences of this involvement.

The induction by cow's milk of T1D in genetically-prone individuals and the mechanism of its diabetogenicity have been clarified [35–47]. They consist basically in cross-reactivity between the peptide ABBOS of bovine serum albumin and the beta cell surface protein p69 [43]. On the other hand, human milk affords protection against a diabetogenic diet by inducing two forms of oral tolerance. A deletional tolerance takes place in the gut-associated lymphoid tissues, where T cell proliferation is suppressed via induction of the tryptophan-degrading enzyme indoleamine-2,3-dioxygenase (IDO) in macrophages [48]: in the absence of tryptophan, T cells are prevented from entering the S-phase [49] and undergo apoptosis [45]. A suppressive tolerance is brought about in the intestinal Peyer's patches by shifting from T helper 1 (Th1) to T helper 2 (Th2) pattern [45, 50]. So, a striking difference in the immunological consequences of human vs. cow's milk in humans explains the opposite effects on the risk of T1D. Moreover, the fact that cow's milk increases the risk of T1D only in genetically predisposed individuals [35, 38–40] is a good example of gene-nutrient interaction.

A high intake of protein of animal origin, beside bovine ABBOS, may be involved in the pathogenesis of autoimmune diabetes in both BB rats and children [51, 52]. Anecdotal reports suggest low T1D incidence in countries with a low protein consumption, and emergence of the disease on adopting high protein intake [51]. Meat and meat products result as risk factors for T1D in children, and this is effected by protein rather than fat [32]. The diabetogenic effect of meat stripped of fat stems from the elicited strong insulinogenic response [53], which is even stronger when protein is coingested with carbohydrates [54]. Early in life, more insulin in beta cells increases the risk of autoimmune TID [55]. This is more likely to happen if in the insulin gene at IDDM2 locus the variable number of tandem repeats (VNTR) is made of the short class I allele [56], which is associated to higher insulin synthesis in beta cells and less insulin in the thymus than class III allele, and hence to lesser tolerance to self-antigen [57]. Therefore, in subjects with VNTR class I allele a diet rich in meat proteins during fetal (maternal diet) or early postnatal life can elicit strong insulin expression in beta cells and increase the risk of T1D, representing another instance of gene-nutrient interaction in the pathogenesis of T1D.

From animal studies, the role of cereals with respect to autoimmune diabetes is rather contradictory. A cereal-based diet is diabetogenic in the BB rat [58], with a mechanism attributable to wheat gluten [58, 59]. This effect, however, can be turned to protective oral tolerance if the cereal-based diet is introduced before weaning [50], a phenomenon described also for other antigens: when administered to mothers during the 18 days of suckling they induce tolerization in the offspring receiving the antigen in the mother's milk [45, 60]. This phenomenon is reminiscent of the rapid increase of the coeliac disease in Sweden in the 1980s, after the introduction of gluten in the infant diet was postponed and fell out of the protective effect of breast milk [61, 62]. And the fact that a high frequency of intake of foods rich in carbohydrate increases the risk of T1D in children seems attributable to the gliadin content [32].

Two recent studies on the influence of infant diet on islet autoimmunity (IA) found nonsignificant association with gluten-containing cereals [63], and IA developed only when gluten was administered after weaning [64]. In both studies the risk of IA after exposure to gluten was

stronger in children with HLA genotypes of susceptibility to TID, indicating once again gene-nutrient interaction. However, another study on the diabetogenicity of wheat and barley in NOD mice [65] concluded that other protein components than gliadin may be immunogenic and diabetes-related, removal of wheat proteins from the diet can reduce diabetes development, and that for this reduction to take place the post-weaning period is particularly important, a high wheat protein containing diet being associated with accelerated diabetes [66]. Therefore, the discrepancy of cereal diabetogenicity in some instances and the contrary in others may reflect, in our opinion, the influence of breast feeding on tolerization: when cereals are introduced under breast milk protection, tolerization can take place, although not every aspect has been clarified in this regard.

Besides, two ecological surveys found negative correlation between cereal consumption and T1D worldwide. In the first one, a Canadian study on dietary starch available to various populations [67], we could calculate a highly significant correlation ($r = -0.605$, $p < 0.001$) in 32 countries; in the second one, carried out by us [27], the result was much the same ($r = -0.640$, $p < 0.001$). It is worth noting the consistency of these results with the observation that among subjects born in period of food shortage, when bread and potatoes formed almost the entire ration [68], a very low frequency of insulin-dependent diabetes was recorded [69].

Before drawing conclusions from the above described observations, some features of nutritional epidemiology must be discussed. Caution is required in interpreting ecological studies, as they can sometimes be misleading, because of the possible occurrence of the so-called ecological fallacy [70], inasmuch as aggregated data for a geographic area as a whole may be only weakly related to the diets of those individuals at risk of disease [71, 72]. The FAO's food balance sheets show for each food item the calculated supply for a given country: the per caput supply for human consumption is then obtained by dividing the respective quantity by the population of the country. Obviously, non-resident population, such as illegal immigrants, tourists, foreign armed forces and other foreigners are not included in the denominator, leading to some degree of overestimate, to which the losses and waste of edible food may also contribute, being not included in the numerator. Moreover, the composition of the food groups may vary substantially among countries, so that their relative role in the pathogenesis of T1D may be different for each country. Nonetheless, many of the correlations of disease rates in populations with the per capita consumption of a specific dietary factor based on disappearance data are remarkably strong: for example, the correlation between meat intake (disappearance) and incidence of colon cancer is 0.85 for men and 0.89 for women [71]. And, besides, food balance sheets represent the only source of standardized data that permit international comparison over time, and can be useful for nutritional studies, provided their results are consistent with those from animal studies and from other sources, and the conclusions are biologically plausible.

With the above discussed reservations, in the present study the dramatic increase in incidence of T1D worldwide seems strongly linked to nutritional habits, especially after the influence of average annual temperature and gross domestic product on T1D incidence has been ruled out by multivariate analysis in a previous [27] and the present study, at variance with an European ecological analysis [73].

The present study adds to the previous ones [22, 27] the new concept that the increasing incidence of T1D worldwide can be explained, at least partly, by the changes in meat consumption. In fact, in our ecological analysis milk consumption remained unchanged and cereals consumption decreased slightly and nonsignificantly from 1961 to 2000, so leaving some doubt about their involvement in the rising incidence of TID. On the contrary, the consumption of meat increased strongly and significantly in the second half of the past century. However, our calculations suggest that this increase wouldn't have been sufficient to make the correlation significant from 1961 to 1983 without the parallel increase in T1D incidence, which is known to be multifactorial in origin [2, 4]. Therefore, other environmental factors beside meat might have contributed to the phenomenon. In any case, the suggestions coming from the present ecological analysis warrant further experimental and case-control studies on the contribution of nutritional factors, and especially meat, to the causation of T1D. But the fact that the correlation between meat consumption and T1D didn't exist in 1961 and became significant in 1983 emphasizes the importance of temporal relation: 'rates may be most appropriately related to dietary data many years earlier' [71], indicating the role of meat more as an inducer than a trigger of T1D.

High meat consumption is known to be associated with ischemic heart disease [74, 75], stroke [76], colon cancer [77], breast cancer [78], type II diabetes [79, 80]. Very low meat intake is associated with significant decrease of all-cause mortality and greater longevity [81]. Vegetarians experience a decreased prevalence of chron-

ic diseases, lower use of medications, including a sharp reduction in use of insulin, and health services and, thus, lower health care costs [76].

The 'cattle culture' is responsible, at least in part, for the environmental, economical, hunger and health crises of human civilization. It is also a contributing factor to the destruction of the tropical rain forests, to the depletion of water supplies and to the climatic changes [82]. Reducing the consumption of beef will proportionally lower all these ailments [83], among which we now include children T1D.

When a nutritional factor is likely to be involved in the pathogenesis of T1D, the dietary exposure to that factor can be manipulated as a means of preventing the disease [84]. In populations with high genetic proneness to TID, such as Sardinians [8] and Finns [85] interaction gene-nutrient is particularly strong. A global strategy for prevention of non-communicable diseases sharing the same risk factors is at present conceivable, and should be extended to the very early periods of life (to pregnant women and to children) through dietary advice, so resulting in preventive effectiveness also for insulin-dependent diabetes mellitus.

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